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Anaesthesia for Caesarean Section in Patients with Cardiac Disease

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Abstract

This review contains material sourced from med-line and pub-med, search year 2002-2004. Material selected was pertaining to common cardiac ailments in pregnancy. Congenital cardiac problems i.e. Tetralogy of Fallot (TOF), Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), Eisenmengers syndrome, valvular heart disease, i.e. mitral stenosis, mitral regurgitation, aortic stenosis and aortic regurgitation are discussed.

Other cardiac conditions associated with pregnancy are pulmonary hypertension and peri-partum cardio-myopathy. Arrhythmias during pregnancy, vary from isolated premature to supra-ventricular and ventricular tachycardia, management is similar to non-pregnant patients.

This review summarizes the current management of a parturient with cardiac disease requiring surgical delivery. Regional anaesthesia techniques are preferred as reflected in the current literature for patient with cardiac disease with minor alterations such as slow establishment of epidural for caesarean section or continuous spinal anaesthesia with very small incremental doses of local anaesthesia, maintaining the patient's SVR with vasopressors and fluid, monitoring of the fluid regimen with CVP and in some cardiac function with Swan Ganz catheter. Patients with Eisenmenger syndrome, pulmonary hypertension, should be advised to avoid pregnancy.

In conclusion with vast advancements in obstetrics care, improvements in cardiac surgery, many patients with cardiac disease can now be safely delivered surgically by skillful anaesthesiologists who are aware of the common potential intra-operative problems and the ability to respond to undesired events immediately.

Introduction

The prevalence of heart disease in pregnancy has remained relatively constant over the last several decades, reported incidence is between 0.4-4.1%¹

Over the past 2 decades, greater awareness of the physiologic burden that pregnancy places on an already compromised cardiovascular system in these parturients, has lead to an early counseling regarding pregnancy, and in some patients it may be advisable to avoid conception.

Pregnant patient with heart disease is a unique chal-

lenge to the obstetrician and anesthesiologist, dealing with high risk parturients and requires a thorough understanding of the impact of pregnancy on the haemodynamic response to the patient's cardiac lesion.¹

The aim of this review is to discuss the current anaesthetic management of parturient with common cardiac conditions, presenting for Caesarean section. Common cardiac lesions seen during pregnancy in our population, range from congenital cardiac defects to peri-partum cardiomyopathy. Understanding the physiology of pregnancy and the patho-physiology of the underlying cardiac disease is important when providing anaesthesia for these high risk obstetric patients. Rheumatic heart disease at present is the most common cardiac disorder in pregnancy, with mitral stenosis (MS) as a single most prevalent lesion.¹

This review attempts to summarize the current status of anaesthesia technique for caesarean section in parturients with underlying cardiac diseases in the Pakistani population. The materials included in this review were sourced by Medline and pub-med search for the year 2004.

1. Congenital Heart Disease (CHD)

Congenital heart disease is becoming the most common source of cardiac problems seen in pregnant patients.² Patients are increasingly likely to survive to child bearing age with the advent of palliative surgery or total correction of their defects and many of them are expected to have an uneventful pregnancy and delivery.

Common congenital cardiac defects are Patent Ductus Arteriosus (PDA), atrial septal defect (ASD) and ventricular septal defect (VSD). Atrial septal defect is the most common cardiac congenital lesion in women of child bearing age, pregnancy is usually well tolerated, and however risk of LVF is increased during pregnancy². Due to increase in the cardiovascular volume during pregnancy there is increase in the atrial volume which may result in bi-atrial enlargement, and super-ventricular dysrhythmias are likely to occur. The anaesthesiologist may be involved in the management of the patients who have had successful surgery during infancy and childhood, with complete repair, asymptomatic with relatively normal intra-cardiac pressures and blood flow pattern or he may be involved in the management of patients with uncorrected lesions, which is challenging and complex. Atrial septal / ventricular septal

defects in pregnancy are often well tolerated during pregnancy.²

When anaesthetizing patients with CHD, using either a regional technique or general anaesthesia, the following factors must be kept in mind; prevention of accidental intravenous infusion of air bubbles, when planning epidural anaesthesia, loss of resistance to saline rather than air should be used to identify the epidural space³, a slow onset of epidural analgesia is preferred, as rapid decrease in systemic vascular resistance (SVR) could result in reversal of shunt with maternal hypoxaemia.² Supplemental O₂ should be given to the patient throughout the procedure if regional technique is used. It is advisable to monitor O₂ saturation as mild hypoxaemia may result in increased pulmonary vascular resistance (PVR) and reversal of shunt flow. Hypercarbia and acidosis should be avoided, as it may result in increased PVR and reversal of shunt flow.

In patients who had successful surgery in infancy or childhood, no special treatment is required. Antibiotic prophylaxis is recommended.

Tetralogy of Fallot (TOF) - constitutes 15% of all congenital cardiac defects (CCD)

TOF is the most common etiologic factor in the right to left shunt.⁴ TOF consists of 4 structural abnormalities, i.e. ventricular septal defect (VSD), right ventricular hypertrophy (RVH), pulmonic stenosis, right ventricular outflow obstruction and overriding of the aorta.

Most pregnant women will have had corrective surgery, which consists of closure of the VSD and widening of the pulmonary tract. This surgery is usually successful but in some patients, a small VSD may reoccur, or progressive hypertrophy of the pulmonary outflow tract may occur slowly over the years.⁵ In patients with history of syncope, polycythemia, decreased arterial O₂ saturation, right ventricular hypertension and congestive cardiac failure (CCF) are particularly at risk.

Patients with successful correction of TOF need no special treatment, except antibiotic prophylaxis and meticulous care to prevent any air entry into the circulation. In patients with uncorrected lesion, anaesthetic considerations must focus on minimizing the haemodynamic changes that would increase right to left shunting. Strict avoidance of decrease in SVR, decrease in venous return or myocardial depression is of paramount importance.

Both techniques regional or general anaesthesia can be used. Choice of induction agents for general anaesthesia should be those agents which would cause least haemodynamic disturbance i.e. narcotic induction with etomidate. Neonatal depression as a result of narcotic induction can be easily treated with endotracheal intubation (ET) tube and no

further medical treatment is required. Regional technique should be used with extreme caution. Single shot spinal anaesthesia should be avoided. Slow induction of epidural is advisable.⁶

Invasive monitoring is mandatory and arterial line or CVP line is preferred to pulmonary artery (PA) catheter, as risk outweighs the benefits.⁷ Complications include pulmonary rupture⁸, thrombosis and in patient with a large VSD or ASD, pulmonary wedge pressure may not reflect left ventricular filling pressure. CVP may be more useful as the right ventricle is at the greatest risk of dysfunction.¹

Eisenmenger Syndrome is a complex combination of cardiovascular abnormalities. It consists of pulmonary hypertension, a right to left extra cardiac shunt and arterial hypoxaemia.² Pregnancy is not well tolerated by patients with this condition. When pregnancy occurs in women with Eisenmenger's syndrome, medical termination is considered safer than any mode of delivery.⁶ Acute arrhythmias are particularly dangerous as these patients have little or no cardiac reserve and need a normal sinus rhythm to keep up with the increased workload. Maternal mortality rate is estimated at 30-50%.

Pathophysiology of Eisenmenger syndrome is described as a chronic, uncorrected right to left shunt, produces right ventricular hypertrophy (RVH), elevated pulmonary artery pressure, and right ventricular (RV) dysfunction. The primary lesion may be either an ASD, VSD or PDA.⁹ The pulmonary and the RV musculature undergoes remodeling in response to the chronic pulmonary volume overload, the high fixed pulmonary artery pressure limits flow through the pulmonary vasculature and when pulmonary artery pressure exceeds the level of systemic pressure, reversal of shunt flow occurs. The initial left to right shunt becomes a right to left shunt, ultimately leading to the Eisenmenger syndrome, which includes the sequelae of arterial hypoxaemia, and RV failure. Clinical manifestations include dyspnoea, clubbing of nails, polycythemia and peripheral oedema and cyanosis. In an established case of Eisenmenger syndrome pulmonary hypertension when permanent, surgical correction of the defect at this stage is unhelpful and may increase mortality.¹⁰

Anaesthetic management of patients with Eisenmenger's syndrome is challenging. If the patient does reach full term, a multidisciplinary approach with close communication between obstetrician, cardiologist and anaesthesiologist is essential. Anaesthetic consideration centres on the avoidance of any decrease in the SVR. Hypotension from any cause can progress to insufficient RV pressure required to perfuse the hypertensive pulmonary arterial bed and may result in sudden death of the patient.

The anaesthetist must be aware of the maternal anticoagulation. Both techniques regional and general anaesthesia may be used, if there are no contraindications to regional block, a titrated epidural anaesthesia is probably the technique of choice.⁶ A slow induction of epidural allows compensation for sympathectomy below the level of block, a dilute solution of phenylephrine may be given as needed to maintain maternal SVR.⁶ O₂ should be administered to all patients undergoing surgery under regional anaesthesia, as O₂ reduces pulmonary vascular resistance, which benefits the patient with Eisenmenger.¹¹ The blood loss should be promptly replaced by crystalloids, colloids, or packed cells. Postpartum autotransfusion may cause intravascular volume overload in these patients. Regional anaesthesia may reduce the risk of postoperative deep vein thrombosis.¹²

Caesarean section can also be conducted under general anaesthesia, but there several disadvantages associated with general anaesthesia⁶ e.g. effects of IPPV on venous return, ventilation/perfusion mismatch, high pulmonary artery pressure, increased shunt through the anatomic defect and myocardial depression by halogenated agents. If slow induction of anaesthesia is used there is a risk of maternal aspiration. Monitoring includes invasive blood pressure monitoring (A-line), and central venous pressure (CVP) monitoring. Pulmonary artery catheter (PA) use is controversial.⁷ It is difficult to position the balloon tipped flow directed catheter into the pulmonary artery and risk of pulmonary artery rupture is always present.⁸ Ampicillin and gentamycin i.v. should be give as prophylaxis against infective endocarditis and repeated eight hourly after the initial dose.

2. Valvular Heart Disease

In general regurgitant valvular lesions are well tolerated during pregnancy, where as stenotic lesions have a greater potential for decompensation. Pregnant patients with valvular heart disease can expect to have worsening of their New York Heart Association (NYHA) functional class⁹, some may develop CCF while others may have adverse foetal outcome i.e. preterm birth or still birth.¹³

i) Mitral stenosis

Mitral stenosis occurs most commonly as a result of rheumatic heart disease. Mitral stenosis is one of the most common valvular lesion in parturient especially in the under developed countries.² Other valvular lesions like mitral regurgitation, aortic stenosis and aortic regurgitation are also associated with rheumatic fever, but are less frequent.

Pregnancy is detrimental to cardiac function in the patient with mitral stenosis (MS) for several reasons. The expanded blood volume can increase the risk of pulmonary

congestion and oedma. The physiological tachycardia in pregnancy decreases the left ventricular (LV) filling time, results in elevated left arterial pressure, can lead to oedema and decreased onward flow of blood, resulting in hypotension, fatigue and syncope.⁹

Normal mitral valve orifice has a surface area of 4-6cms² and symptoms develop when area is reduced to 2cms² or less. Mitral valve stenosis prevents emptying of the left atrium (LA), with increased left atrial and pulmonary artery pressure, resulting in dyspnoea, haemoptysis and pulmonary oedema.

Anaesthetic considerations are to maintain a slow heart rate, venous return and SVR, avoid aorto-caval compression, treat atrial fibrillation (AF) aggressively, try and maintain sinus rhythm, prevent pain, hypoxaemia, hypercarbia and acidosis as these can increase PVR. Both general anaesthesia and regional techniques have been used. Anaesthetic options for caesarean section in patients with mitral stenosis, must take into account the additional potential hazards of marked fluid shifts secondary to anaesthesia technique and operative blood loss.

Epidural anaesthesia is preferred in patients with mitral stenosis as the on-set of blockade is slow therefore the haemodynamics are more controllable. Prophylactic ephedrine administration should be avoided. If a need for vaspressor arises, the drug of choice in patients with MS is low dose phenylphrine.

General anaesthesia also provides a very stable haemodynamic course, if the cardiovascular effects associated with laryngoscopy and intubation and oral suction are minimized. Induction agent should not produce wide swings in the haemodynamics. Etomidate is a suitable induction agent. A beta-blocker such as esmolol and a modest dose of opioid should be administered before or during the induction of general anaesthesia. Oxytocin should be used with care, a dilute solution instead of bolus dose is recommended, and emergence must be carefully controlled to avoid tachycardia.

ii) Mitral Regurgitation

Pure mitral regurgitation is rarely a problem. Ischemic papillary muscle disease, myxomatus degeneration, rheumatic fever and endocarditis are common causes, and most patients with MR tolerate pregnancy well.

Regurgitation of blood through an incompetent mitral valve results in chronic volume over load and dilatation of the LV. Regurgitation may be acute or chronic. In the acute type, there is acute pulmonary congestion and pulmonary edema results. If the patient survives this episode of acute mitral regurgitation, pulmonary artery pressure

continues to increase and right heart failure occurs. Pregnancy induces a hyper-coagulable state and systemic embolism may occur in 20% patients with mitral regurgitation.

Regional or general anaesthesia may be instituted. Epidural anaesthesia prevents increase in SVR, promotes forward flow of blood and helps to prevent pulmonary congestion.¹ Slow induction of epidural is indicated.

If general anaesthesia is required, ketamine and pancuronium are desirable agents in these patients.¹ Atrial fibrillation (AF) must be treated promptly, and haemodynamic instability associated with AF warrants immediate cardioversion. Invasive (intra-arterial) BP monitoring, and pulmonary artery catheter monitoring are advisable.

Antibiotic with pre-medication is recommended, as these patients are prone to infective endocarditis. Primary considerations are to maintain slightly increased heart rate, to prevent increase in SVR, increase in the central blood volume, and prevent hypoxemia, hypercarbia, acidosis which may increase PVR, avoid aortocaval compression and myocardial depression.

iii) Aortic stenosis

(AS) rarely complicates pregnancy. The natural history of this lesion, require 3-4 decades to reach severity to produce symptoms.² However, bicuspid aortic valve is the most common congenital anomaly of the heart.⁹ The pathophysiology of severe AS entail a narrowing of the valve to less than 1 cm² associated with a trans-vascular gradient of 50mmHg with significant increase in after load to the LV. A valvular gradient which exceeds 100mmHg, there is an increased risk of myocardial ischemia as the LV hypertrophies significantly.²

In aortic stenosis transvascular gradient increases progressively throughout pregnancy, due to increasing blood volume and decreasing SVR.

Anaesthetic management in AS is to avoid tachycardia, and bradycardia, maintain intravascular volume and venous return, avoid aortocaval compression, and myocardial depression, maintain a normal heart rate as a slow heart rate decreases cardiac output (CO). Tachycardia may decrease time for coronary perfusion of the hypertrophied LV. Arrhythmias are not well tolerated and should be promptly treated. Patients with trans-vascular gradient more than 50mmHg with symptomatic AS should have invasive monitoring i.e. A-line and PA catheter in place.

General or regional anaesthesia is used. Traditionally epidural analgesia is contraindicated due to the risk of fall in SVR, resulting in hypotension, poorly tolerated in patients with a fixed cardiac output. Neuraxial

block for aortic stenosis has become an accepted technique but remains controversial.^{1,4} Regional anaesthesia for caesarean section in patients with aortic stenosis has been described in several reports.¹⁴

General Anaesthesia should be accomplished with the same caution that applies to MS. Drugs of choice are a combination of etomidate and modest dose of opioids with succinylcholine for rapid sequence intubation. Myocardial depression associated with volatile anaesthetic agents should be avoided. Oxytocin should be avoided as it is known to cause marked vasodilation, with hypotension. The drug of choice for uterine contraction is ergometrine at the end of delivery.

PA catheter monitoring is controversial⁷, as it entails a high risk of ventricular arrhythmias and cardiovascular collapse.¹ CVP monitoring is desirable and should be maintained at a high normal level to protect cardiac output during unexpected peri-partum haemorrhage.

iv) Aortic insufficiency

This may be congenital or acquired. Rheumatic fever is a cause in 75% of cases.

The pathophysiology is of chronic volume overload of the LV, with hypertrophy and dilatation and increase in LV End Diastolic Volume (LVEDV), decrease in ejection fraction (EF) and signs and symptoms of pulmonary edema. Patients with aortic insufficiency tolerate pregnancy well as pregnancy results in a modest increase in heart rate. Anaesthetic considerations focus on minimizing pain to prevent catecholamine - induced increases in SVR and avoid bradycardia, which may increase regurgitant flow.

Epidural anaesthesia is preferred as it decreases the after-load, and prevents increases in SVR and acute LV volume overload in these patients. If the patient is on anticoagulant, RA poses a risk of epidural / spinal haematoma.¹

General anaesthesia may be induced with etomidate to prevent severe haemodynamic swings, followed by intubation of the trachea with suxamethonium. Remi-fentanyl is the drug of choice to provide analgesia. It is used as an infusion during induction and maintenance of anaesthesia and provides haemodynamic stability. Neonatal respiratory depression is known to occur with remi-fentanyl. It is treated with endotracheal intubation and no further medical management is required for the neonate.¹⁵

v) Congenital Mitral Valve Prolapse

(MVP) is much more common among pregnant women, and the reported incidence is 10-17% of all pregnancies.¹⁶ Women with MV prolapse usually tolerate pregnancy well.

Pathophysiology is a primary idiopathic MVP characterized by a redundant valve that prolapses into the ventricle during systole. It is a benign condition and most patients are asymptomatic, however some may develop symptoms of chest pain, dyspnoea, weakness and palpitation.

Anaesthetic consideration is to avoid decrease in cardiac output, heart rate and LV End Diastolic Pressure (LVEDP) as this can exaggerate the prolapse.

Both regional and general anaesthesia can be instituted. Regional anaesthesia is an excellent choice for caesarean delivery.¹ Epidural anaesthesia is the technique of choice. Slow induction with low dose local anaesthetic agent and an opioid is advised.

During general anaesthesia all sympathomimetic agents should be avoided, because of high incidence of arrhythmias. Hypotension can be treated with small boluses of phenylephrine.

vi) Prosthetic valves

A pregnant patient with a prosthetic valve is at a high risk of foetal and maternal complications. Maternal complications include thrombo-embolic phenomena, valve failure and bacterial endocarditis. Foetal complications include foetal haemorrhage due to maternal anticoagulation and teratogenicity. Porcine heterografts are best choice for women of child bearing age who wish to become pregnant. Both regional and general anaesthesia can be given safely.

Regional anaesthesia is preferred in these patients but the chronic use of heparin may result in thrombocytopenia and continuous anticoagulant therapy is a contraindication for regional analgesia.²

When general anaesthesia is required in these anticoagulated patients, residual valvular or myocardial dysfunction will influence the choice of anaesthetic drugs and the use of additional monitoring i.e. CVP, PA catheter and A-line are recommended.

3. Primary Pulmonary Hypertension

Pulmonary hypertension and pregnancy is a lethal combination.¹⁷ Patients with this condition are advised to avoid pregnancy, preferably by tubal ligation as contraceptive drugs are shown to accelerate the progression of the disease.¹⁷

Main feature of this syndrome is raised pulmonary artery pressure, unlike the Eisenmenger syndrome, the pulmonary vascular tone in this condition responds to vasodilator agents.¹

Anaesthetic management is similar to that of the Eisenmenger syndrome. Elective caesarean section is the

preferred method of delivery.¹⁸ Both regional and general anaesthesia can be used for caesarean delivery. For regional anaesthetic technique using a slow induction epidural anaesthesia is advised. Vasopressors are only used if absolutely necessary, as they increase pulmonary artery pressure.¹⁹ A continuous spinal technique (CSA) has been described using a catheter and incremental injection of local anaesthesia producing a predictable block and a lower incidence of hypotension.^{20,21} Recently the use of nitric oxide (NO), a potent vasodilator has become popular for patients with primary pulmonary hypertension. There are few reports of its use in pregnancy.¹

4. Peripartum Cardio-Myopathy (PPCM)

PPCM was first defined in 1971 as symptoms of heart failure that become apparent in the last month of pregnancy or within 5 months postpartum in patients who have no pre-existing heart disease and no other obvious etiology for heart failure.⁹ Recently echo-cardiographic criteria including EF less than 45% and diastolic dimension greater than 2.72cm/m² for the diagnosis were established by Hibbard et al. Peri-partum cardio-myopathy is a serious myocardial disease of a dilative nature where the patient presents with heart failure in the 3rd trimester of pregnancy. Reported incidence is 1 in 4000 and 1 in 10,000²² and mortality rate is 18%-50%.²² It could be Viral, autoimmune or toxic in nature. Other factors e.g. nutritional deficiencies, small vessel coronary artery disease, myocarditis, pregnancy related exacerbation of the pre-existing cardio-myopathy of some form, may play a role in the etiology.¹ Initially, symptoms are of mild upper respiratory tract infection, chest congestion and fatigue, these symptoms can progress to rapid florid cardiac failure with biventricular hypokinesia. Principles of anaesthetic management are same as those for severe cardio-myopathy. Primary goals are to avoid myocardial depressants, and cautious fluid management with judicious use of diuretics and vasodilators, (maintenance of normal heart rate and sinus rhythm). Both regional and general anaesthesia can be used with extreme cautions.

Very recently continuous spinal anaesthesia (CSA) was successfully employed as an anaesthetic technique for caesarean section delivery in PPCM. Using low dose local anaesthesia and opioids combination which is slowly titrated²³, CSA appears to offer more haemodynamic stability than a single dose of spinal anaesthesia for caesarean section.¹⁹ Invasive monitoring is required, including PA catheter. A-line is necessary when using general anaesthesia. Potential hazards such as increased pulmonary artery pressure during laryngoscopy and intubation, the adverse effects of IPPV on venous return and the negative inotropic

effects of certain anaesthetic agents should be kept in mind. These effects can however be minimized by the use of narcotic based induction and maintenance of anaesthesia.

5. Maternal arrhythmias during pregnancy

Management of arrhythmias during pregnancy is similar to that in the non-pregnant patient.¹

Catecholamine sensitive ventricular tachycardia (VT)

Majority of VTs are due to re-entry, and may appear for the first time during gestation.²⁴ Patients with a prior history of VT should continue their anti-arrhythmic medication throughout pregnancy. Slow incremental CSE is the recommended technique²⁴ of choice.

Congenital heart block and bradyarrhythmias

If congenital heart block is recognized in a pregnant woman, cardiac consultation should be taken, to determine whether there is need of a pacemaker. A pacemaker is indicated in patients with symptoms, when Q-T interval is prolonged or there is left atrial enlargement. Equipment as CVP access tray, and trans-venous pacing wires should be ready at patient's bedside during caesarean delivery, in the event of rapid intervention.²⁵ Epidural analgesia is recommended for caesarean section delivery.

Postoperative period in parturients with cardiac disease

In the postoperative period, patients with severe cardiac dysfunction delivered by Caesarean section should be kept in the High Dependent Unit (HDU) / intensive care unit (ICU) for aggressive monitoring of fluid therapy, oxygen saturation and haemodynamics. During the first 24-72 hours significant fluid shift occurs, which may lead to CCF. Adequate post-operative analgesia should be provided in the form of continuous epidural analgesia or patient controlled IV analgesia. Early ambulation to minimize the risk of deep venous thrombosis and paradoxical embolization should be weighed against the risk of cardiovascular stress.²⁶

Foetal and maternal outcome in Caesarean delivery in patients with cardiac disease

The optimal management of these patients requires cooperative efforts of the obstetrician, cardiologist and the anaesthesiologist involved in the care of these high risk patients.^{26,27} Classification of these patients according to the New York Heart Association (NHA) correlates best with the maternal outcome.²⁸ Mortality rate of less than 1% is reported in Class I and II while in class III and IV it is between 5-15%.²⁹

Summary

The current status of a parturient with cardiac disease has become safer with improvement in treatment and management. Patients with cardiac disease were strongly discouraged in the past from becoming pregnant, now with vast improvement in cardiac care and advances in reproductive technology, more women with cardiac disease are planning pregnancy. The management of parturients with severe cardiac ailments is not anymore "one man's show".²⁶ The cardiologist, obstetrician and the anaesthesiologist should jointly analyze and discuss the cardiac problem and to make a rational choice of the management. The skill and experience of the anaesthesiologist on common potential intra-operative problems, the ability to respond quickly to haemodynamic disturbances are far more important than the specific technique or agent used.

The advantage of regional anaesthesia is that the patient can report any symptoms as palpitations, chest pain and shortness of breath, so that prompt action can be taken.²⁶ Regional anaesthesia should be established with low dose of LA, and an opioid. The induction of the epidural should be slow to prevent acute episodes of hypotension. If general anaesthesia is required, the standard technique of rapid sequence induction is employed, which does little to blunt the stress response.

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